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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	
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12/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,394	STAMLER ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 9-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pages 09/04/09 and 09/18/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is office action is in response to applicant's request for continued examination filed on September 18, 2009.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Status of Claims

Cancellation of claims 7-8 and amendment of claim 1, and addition of claims 9-15 is acknowledged.

Claims 1 and 9-15 are currently pending and are the subject of this office action.

Claims 1 and 9-15 are presently under examination.

Priority

The present application is a 371 of PCT/US02/36138 filed on 12/02/2002, and claims priority to provisional application No. 60/336,175 filed on 12/06/2001.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (New Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-15 recite the limitation "vasodilator". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103 (New Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216) in view of Cederqvist et. al. (Biochemical Pharmacology (1994), 47:1047-1053).

Claim 1 recites a method for preventing necrosis in a pedicle flap or in any microvascular surgery, comprising topically applying to pedicle or other source of blood supply, a therapeutically effective amount of a composition comprising an NO donor that causes formation of nitrosothiol in tissue.

Claim 9 further limits claim 1, wherein the NO donor that causes formation of nitrosothiol in tissue contains alkyl nitrite of molecular weight up to 10,000.

Claim 10 further limits claim 9, wherein the alkyl nitrite is ethyl nitrite.

For claims 1 and 9-10, Kreidstein et. al. teach the use of topical nitrovasodilators or NO donors (Acetylcholine (ACh) and nitroglycerin (NTG)) for prevention and (or) treatment of skin flap ischemia (i.e. ischemic necrosis) (see abstract, last 4 lines). Kreidstein further teaches that Ach is generally described as an endothelium dependent vasodilator that produces vasodilatation by stimulating the release of a relaxing factor (NO) from endothelium cells (see page 1212, under Discussion, last paragraph). Also, NTG is an endothelium-independent vasodilator that acts directly on vascular smooth muscle by providing an exogenous source of NO, supplanting endothelium-derived NO (see page 1213, end of left column, beginning of right Colum). Finally, Kreidstein teaches that topical NTG has been reported effective in augmentation of skin blood flow and viability in arterial skin flaps in the rat and pig (see page 1215, left column). In summary, Kreidstein teaches that NO plays a role in the pathophysiology and pharmacology of the skin flap, and that compounds that can donate NO directly (i.e. NTG) or indirectly (i.e. ACh) are effective in reducing the risk of necrosis in a pedicle flap.

Kreidstein et. al. do not teach the use of an NO donor that causes formation of nitrosothiol in tissue, wherein the NO donor that causes formation of nitrosothiol in tissue is an alkyl nitrite of molecular weight up to 10,000, and wherein the alkyl nitrite of molecular weight up to 10,000 is ethyl nitrite. However, Cederqvist et. al. teach that ethyl nitrite (MW=75.07) and organic nitrites in general are NO donors (see abstract).

Since Kreidstein teaches a method of treating or preventing skin flap necrosis with a NO donor, and since Cederqvist teaches that ethyl nitrite is a NO donor, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any NO donor) for another (ethyl nitrite) with an expectation of success, since the prior art establishes that both function in similar manner.

Cederqvist is silent regarding the molecular weight of ethyl nitrite being less than 10,000. However, this is an inherent property of alkyl nitrite which has molecular weight of 75.07.

Kreidstein and Cederqvist are silent regarding: "an NO donor (ethyl nitrite) that causes formation of nitrosothiol in tissue". However, this property (formation of nitrosothiol in tissue by ethyl nitrite) does not result in a manipulative difference with the prior art and will necessary be present in the method made obvious by Kreidstein and Cederqvist (see above), since the same compound: ethyl nitrite is being used for the same purpose: preventing skin flap necrosis. In other words, products of identical or similar composition cannot exert mutually exclusive properties when administered under the same circumstances. MPEP 2112 I states: "The discovery of a previously

unappreciated property of a prior art composition or a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer".

All this would result in the practice of claims 1 and 9-10 with a reasonable expectation of success.

Claims 1 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216), in view of Stamler et. al. (US 5,770,645).

Claim 1 recites a method for preventing necrosis in a pedicle flap or in any microvascular surgery, comprising topically applying to pedicle or other source of blood supply, a therapeutically effective amount of a composition comprising an NO donor that causes formation of nitrosothiol in tissue.

Claims 11 further limits claim 1, wherein the NO donor that causes formation of nitrosothiol in tissue contains an S-nitrosothiol.

Claim 12, further limits claim 11, wherein the S-nitrosothiol is cyclodextrin NO.

For claims 1 and 11-12, Kreidstein et. al. teach the use of topical nitrovasodilators or NO donors (Acetylcholine (ACh) and nitroglycerin (NTG)) for prevention and (or) treatment of skin flap ischemia (i.e. ischemic necrosis) (see abstract, last 4 lines). Kreidstein further teaches that Ach is generally described as an endothelium dependent vasodilator that produces vasodilatation by stimulating the release of a relaxing factor (NO) from endothelium cells (see page 1212, under Discussion, last paragraph). Also, NTG is an endothelium-independent vasodilator that

acts directly on vascular smooth muscle by providing an exogenous source of NO, supplanting endothelium-derived NO (see page 1213, end of left column, beginning of right Colum). Finally, Kreidstein teaches that topical NTG has been reported effective in augmentation of skin blood flow and viability in arterial skin flaps in the rat and pig (see page 1215, left column). In summary, Kreidstein teaches that NO plays a role in the pathophysiology and pharmacology of the skin flap, and that compounds that can donate NO directly (i.e. NTG) or indirectly (i.e. ACh) are effective in reducing the risk of necrosis in a pedicle flap.

Kreidstein et. al. do not teach the use of an NO donor that causes formation of nitrosothiol in tissue, wherein the NO donor that causes formation of nitrosothiol in tissue is an S-nitrosothiol, and wherein the S-nitrosothiol is cyclodextrin NO. However, Stamler teaches that S-nitrosylated cyclodextrins (a type of cyclodextrin NO) are NO donors (see column 2, first paragraph).

Since Kreidstein teaches a method of treating or preventing skin flap necrosis with a NO donor, and since Stamler teaches that cyclodextrin NO is a NO donor, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any NO donor) for another (cyclodextrin NO) with an expectation of success, since the prior art establishes that both function in similar manner.

Kreidstein and Stamler are silent regarding: "an NO donor (cyclodextrin NO) that causes formation of nitrosothiol in tissue". However, this property (formation of nitrosothiol in tissue by cyclodextrin NO) does not result in a manipulative difference

with the prior art and will necessary be present in the method made obvious by Kreidstein and Stamler (see above), since the same compound: cyclodextrin NO is being used for the same purpose: preventing skin flap necrosis. In other words, products of identical or similar composition cannot exert mutually exclusive properties when administered under the same circumstances. MPEP 2112 I states: "The discovery of a previously unappreciated property of a prior art composition or a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer".

All this would result in the practice of claims 1 and 11-12 with a reasonable expectation of success.

Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216), in view of Wang et. al. (Journal of Cardiovascular Pharmacology (2000) 35:73-77).

Claim 1 recites a method for preventing necrosis in a pedicle flap or in any microvascular surgery, comprising topically applying to pedicle or other source of blood supply, a therapeutically effective amount of a composition comprising an NO donor that causes formation of nitrosothiol in tissue.

Claim 13, further limits claim 1, wherein the NO donor that causes formation of nitrosothiol in tissue contains a metal nitrosyl.

For claims 1 and 13, Kreidstein et. al. teach the use of topical nitrovasodilators or NO donors (Acetylcholine (ACh) and nitroglycerin (NTG)) for prevention and (or) treatment of skin flap ischemia (i.e. ischemic necrosis) (see abstract, last 4 lines). Kreidstein further teaches that Ach is generally described as an endothelium dependent vasodilator that produces vasodilatation by stimulating the release of a relaxing factor (NO) from endothelium cells (see page 1212, under Discussion, last paragraph). Also, NTG is an endothelium-independent vasodilator that acts directly on vascular smooth muscle by providing an exogenous source of NO, supplanting endothelium-derived NO (see page 1213, end of left column, beginning of right Colum). Finally, Kreidstein teaches that topical NTG has been reported effective in augmentation of skin blood flow and viability in arterial skin flaps in the rat and pig (see page 1215, left column). In summary, Kreidstein teaches that NO plays a role in the pathophysiology and pharmacology of the skin flap, and that compounds that can donate NO directly (i.e. NTG) or indirectly (i.e. ACh) are effective in reducing the risk of necrosis in a pedicle flap.

Kreidstein et. al. do not teach the use of an NO donor that causes formation of nitrosothiol in tissue, wherein the NO donor that causes formation of nitrosothiol in tissue contains a metal nitrosyl. However, Wang teaches that metal nitrosyl are NO donors (see title and abstract).

Since Kreidstein teaches a method of treating or preventing skin flap necrosis with a NO donor, and since Wang teaches that metal nitrosyl are NO donors, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in

the art to substitute one functional equivalence (any NO donor) for another (metal nitrosyl) with an expectation of success, since the prior art establishes that both function in similar manner.

Kreidstein and Wang are silent regarding: "an NO donor (metal nitrosyl) that causes formation of nitrosothiol in tissue". However, this property (formation of nitrosothiol in tissue by metal nitrosyl) does not result in a manipulative difference with the prior art and will necessary be present in the method made obvious by Kreidstein and Wang (see above), since the same compound: metal nitrosyl is being used for the same purpose: preventing skin flap necrosis. In other words, products of identical or similar composition cannot exert mutually exclusive properties when administered under the same circumstances. MPEP 2112 I states: "The discovery of a previously unappreciated property of a prior art composition or a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer".

All this would result in the practice of claims 1 and 13 with a reasonable expectation of success.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216) in view of Cederqvist et. al. (Biochemical Pharmacology (1994), 47:1047-1053) as applied to claims 1 and 9-10 above, and further in view of Chahn et. al. (Otolaryngol. Head Neck Surg. (1997) 117:93-8, cited by Applicant).

Claim 14 further limits claim 1, wherein the composition further comprises lidocaine.

Kreidstein and Cederqvist teach all the limitations of claim 14, except for the presence of lidocaine in the composition. However, Chahn teaches that lidocaine has been effectively used for the prevention of flap death (flap necrosis) in reconstructive surgery (see abstract and discussion on pages 93-94).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to prevent flap necrosis combining two compositions (an NO donor like ethyl nitrite and lidocaine) each of which is taught by the prior art to be useful for the same purpose (preventing flap necrosis), in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). All this would result in the practice of claim 14 with a reasonable expectation of success.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216) in view of Cederqvist et. al. (Biochemical Pharmacology (1994), 47:1047-1053) as applied to claims 1 and 9-10 above, and further in view of Stamler et. al. (US 5,770,645).

Claim 15, further limits claim 1, wherein the composition (NO donor) is incorporated in a therapeutically effective amount in a gel containing from 1 micromolar to 100 micromolar nitrosylated polythiolated cyclodextrin.

Kreidstein and Cederqvist teach all the limitations of claim 15, except for the incorporation of the composition of a therapeutically effective amount in a gel containing from 1 micromolar to 100 micromolar nitrosylated polythiolated cyclodextrin. However, Stamler teaches that nitrosylated polythiolated cyclodextrins are NO donors (see abstract and column 2, first paragraph). Stamler further teaches that S-nitrosylated cyclodextrins can form complex with a suitable nitrosylating agent (see column 7 lines 58-67). The recommended dosages of S-nitrosylated cyclodextrins can be from 10 mg/kg/day to about 1,000 mg/kg day, and the compound can be administered by an appropriate route in a single or multiple doses (see column 12, lines 2-12).

Since Kreidstein teaches a method of treating or preventing skin flap necrosis with a NO donor, and since Stamler teaches that S-nitrosylated cyclodextrins are NO donors, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any NO donor) for another (cyclodextrin NO), and as such be able to treat or prevent skin flap necrosis with an S-nitrosylated cyclodextrin, with an expectation of success, since the prior art establishes that both function in similar manner.

It would have been further obvious for a person of ordinary skill in the art to prevent flap necrosis combining two compositions (an NO donor like ethyl nitrite and an S-nitrosylated cyclodextrin) each of which is taught by the prior art to be useful for the

same purpose (preventing flap necrosis), in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Since Stamler teaches recommended dosages of S-nitrosylated cyclodextrins can be from 10 mg/kg/day to about 1,000 mg/kg day It would have been further obvious to administer a 1 micromolar to 100 micromolar of S-nitrosylated cyclodextrins since a *prima facie* case of obviousness exists (see MPEP 2144.05 I) where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.) .

All this would result in the practice of claim 15 with a reasonable expectation of success.

Response to Applicant's arguments related to the above 103 rejection

Applicant's arguments have been fully considered but are not persuasive. Note: Applicant's arguments regarding the Davies reference, used as prior art in the 103

rejection in the prior office action dated March 18, 2009 have been omitted, since the Davies reference is no longer being used as prior art in the instant 103 rejection.

Applicant argues that:

Davies and Kreidstein merely describe the use of nitroglycerin (along with other compounds) to induce vasodilation. Neither, Davies or Kreidstein describe the use of an NO donor that causes nitrosothiol formation in tissue for preventing skin flap necrosis during surgery, as required by the instant claims, as nitroglycerin (NTG) is not a member of this specific class of NO donors, since it is not capable of directly forming nitrosothiol. That is, NTG, while considered an NO donor, has a completely different biochemical and physiological profile than NO donors which form nitrosothiols. Cederqvist fails to cure the deficiencies in the teachings of Davies and Kreidstein. Cederqvist merely describes specific types of organic nitrites, including NTG, that can serve as NO donors.

There is no evidence that the skilled artisan, reading the combination of these references, would swap any one NO donor for any other NO donor (as asserted by the Examiner) to reach the present invention with predictable results.

In fact, Davies and Kreidstein both teach that a significant amount of unpredictability exists regarding the efficacy of different types of vasodilator compositions, including nitrovasodilators, in mediating skin flap survival.

Kreidstein teaches the use of nitroglycerin to study endothelium independent vasodilation in human skin flaps using an isolated, perfused skin flap model, and

suggests that nitrovasodilators, such as nitroglycerin, may be used to prevent skin flap ischemia. However, Kreidstein teaches away from the Examiner's assertion that any NO donor would be interchangeable for any other as the Authors state that the efficacy for nitroglycerin intervention is unclear, citing evidence where topical nitroglycerin was both effective and ineffective in augmenting skin flap viability. Kreidstein additionally warns that "further studies on the role of NO in the pathophysiology and pharmacology of the skin flap are required".

Based on the foregoing, the skilled artisan reading the combination of Davies, Kreidstein and Cederqvist as a whole, as required, would not exchange NTG, as taught by these references, for an NO donor that generates nitrosothiol formation in tissue to reach the present invention with predictable results.

Examiner's response: Examiner's response: Kreidstein teaches that NTG is an NO donor, and they also demonstrated that NTG induced endothelium independent vasodialtion in isolated perfused human skin flaps (see Fig.9) and this result suggests that there may be a role for topical application of nitovasodialtors or NO donors in ischemic skin flaps where EDFR/NO activity is compromised, to prevent and/or treat skin flap ischemia (see page 1215, first full paragraph on right column). They further say that: "the efficacy for this pharmacologic intervention (to prevent and/or treat skin flap ischemia with NTG) is unclear at the present time" (see same paragraph). However they further say: "**topical NTG has been reported effective in augmentation of skin blood flow and viability in arterial skin flaps (i.e. axial-pattern skin flaps) in the rat and pig**. On the other hand, it has been reported that topical NTG treatment did not

have any significant effect on skin viability in rat random pattern skin flaps. Obviously, further studies on the role of NO in the pathophysiology and pharmacology of the skin flap are required". What Kreidstein is saying is that there are already cases reported in the prior art wherein NTG as demonstrated to be effective in treating and/or preventing necrosis of skin flaps. The fact that there are other cases, in which NTG did not show efficacy, does not prevent the skilled in the art to be motivated to try other NO donors, besides NTG, in order to achieve the same or better and more consistent results. The prior art is full of contradictory results. These results will not prevent the skilled in the art to further explore other options in order to verify and or improve upon the positive results, since negative results can be the consequence of incorrect experimental conditions, incorrect interpretation of results, etc; and not an indication that the method itself is ineffective.

The fact that NTG is not known to generate nitrosothiol in tissue, does not prevent the skilled in the art to look for other NO donors, even though they may deliver NO by a different mechanism than NTG. The fact is that Kreidstein clearly teaches that NTG is effective in treating and/or preventing necrosis skin flaps (see above discussion), will motivate the skilled in the art to replace NTG with any other NO donor, regardless of its mechanism of action, because at the time of the invention, there was nothing in the prior art that would suggest that the efficacy of treating and or preventing necrosis of skin flaps will be influenced by the mechanism of action of the NO donor. There is nothing in the prior art that teaches away from using any NO donor regardless of its mechanism of action. There is nothing in the prior art that teaches or suggests

that certain NO donors are preferred over others. The teachings clearly show that NO donors are effective in treating and/or preventing necrosis of skin flaps. So, at the time of the invention, it would have been expected that any NO donor, regardless of tits mode of delivering NO, will be able to prevent and/or treat necrosis of skin flaps with a reasonable expectation of success.

Applicant further argues: Additionally, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made also involves factual findings with respect to secondary considerations, including failure of others and superior/unexpected results. See Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

The present invention provides superior properties not taught or suggested by the combination of Davies, Kreidstein and Cederqvist. As evidenced by the variable and inconsistent results described in Davies and Kreidstein, not all vasodilating compounds were capable of inducing vasodilation to mediate skin flap survival, and nitroglycerin was unable to assert its effects on all types of skin flaps (e.g., random-pattern, axial-pattern and free vascularized flaps) and across all species.

Examiner's response: Applicant was not able to demonstrate any superior or unexpected result with the compounds of the instant application as compared to the ones in the prior art (i.e. NTG), since Applicant did not present any side by side comparison of NTG and the instant compounds in all types of skin flaps.

Applicant further argues: More importantly, the biochemical and physiological profile of NTG renders this compound ineffective at preventing necrosis in a pedicle flap, or in any microvascular surgery, when compared to the claimed NO donors which directly generate nitrosothiols in the tissue.

The data described in Kreidstein and Davies demonstrating any effectiveness of nitroglycerin in preventing flap necrosis is mischaracterized and inapplicable to the instant invention. That is, the isolated perfusion and ischemia models utilized by Kreidstein and Davies respectively, are not physiologically relevant models for studying the prevention of skin flap necrosis during surgery or under physiological conditions because these models lack the essential components for skin flap survival: blood vasculature and red blood cells.

Examiner's response: Kreidstein teaches that: **"topical NTG has been reported effective in augmentation of skin blood flow and viability in arterial skin flaps (i.e. axial-pattern skin flaps) in the rat and pig"** (see page 1215, left column, lines 10-13). According to Davies et. al. (Annals of Plastic Surgery (1998) 40:630-636) which is cited for evidentiary purposes only and not as part of the rejection itself, "axial-pattern skin flaps are characterized by a direct arterial supply and venous drainage. These flaps are fundamentally more reliable and provide more consistent flap healing. This is due in part to the fixed, direct blood supply to the skin flap" (see page 631, left column, second paragraph).

Applicant further argues: It is well known in the art that NTG is an inefficient NO donor because it first requires biotransformation by a mitochondrial enzyme in order to release NO. This required mitochondrial enzyme is not present in blood, as red blood cells do not contain mitochondria. Even if it the enzyme were present, the skilled artisan would be readily aware that nitric oxide is inactivated in blood. Thus, a compound that merely generates NO, such as NTG, would not be effective to prevent skin flap necrosis in a surgical setting where the presence of blood flow in the skin flap is essential to flap survival.

Examiner's response: as discussed above Kreidstein provides data from the prior art that shows that NTG is effective in treating and/or preventing necrosis of skin flaps wherein there is a direct blood supply to the skin flap ("**topical NTG has been reported effective in augmentation of skin blood flow and viability in arterial skin flaps (i.e. axial-pattern skin flaps) in the rat and pig**" (see page 1215, left column, lines 10-13)), which contradicts the above Applicant's speculative conclusion that: a compound that merely generates NO, such as NTG, would not be effective to prevent skin flap necrosis in a surgical setting where the presence of blood flow in the skin flap is essential to flap survival.

Besides, two of the references provided by Applicant (Chen et. al. PNAS 99:830-8311 (2002), Chen et. al. PNAS 102:12159-12164 (2005) have post-filing date and as such can not be considered prior art. Also, there is nothing in those references that demonstrates (even post filing) that NTG will not be effective in the treatment and/or prevention of necrosis in skin flaps as demonstrated by Kreidstein.

Applicant finally argues: In contrast, nitrosothiol generating compounds, such as those claims, are much more effective than NTG, or other types of NO donors, in mediating skin flap necrosis in a physiological environment. Specifically, the direct formation of nitrosothiol by these compounds prevents their immediate inactivation by blood and creates reservoirs of NO activity in the tissue, thereby providing a longer biological activity profile than other types of NO donors. Additionally, nitrosothiol generating compounds, as claimed, are more effective than compounds such at NTG, as these nitrosothiol generating compounds dilate both arteries and veins, whereas most other NO donor compounds, such as nitroglycerin, only have venous activity. These unexpected and superior properties of the claimed nitrosothiol forming NO donors is not taught or suggested by the combination of Davies, Kreidstein and Cederqvist.

Examiner's response: Applicant is just presenting arguments without any experimental fact to support them. Applicant is simply speculating that the instant disclosed compounds would be superior to NTG because some mechanistic differences between the two groups. However, as reasonable as it might sound, mere speculation is not evidence that these compounds will behave differently or would be more efficacious than the other. Applicant did not provide any side by side comparison between NTG and the NO donors disclosed in the instant Application for the treatment and/or prevention of necrosis of skin flaps, in order to prove that there are any unexpected results.

Withdrawn Rejections and/or Objections

Claim 1 previously rejected under 35 USC 103 (a)

Due to applicant's amendment of claim 1 the 35 USC 103(a) rejection is now moot.

Rejection under 35 USC 103 (a) is withdrawn.

However, a new rejection under 35 USC 103 (a) necessitated by amendment (see above) was applied.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

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/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
November 17, 2009

/Gollamudi S. Kishore/

Primary Examiner, AU 1612